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Original Article

Prediction of acute pancreatitis risk based on PIP score in children with cystic fibrosis

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Abstract

Background: Currently no tools to predict risk of acute (AP) and recurrent pancreatitis (ARP) in children with cystic fibrosis (CF) are available. We assessed the prevalence of AP/ARP and tested the potential role of Pancreatic Insufficiency Prevalence (PIP) score in a cohort of children with CF.
Methods: We identified two groups of children, on the basis of presence/absence of AP/ARP, who were compared for age at diagnosis, clinical features, genotypes and sweat chloride level. PIP score was calculated for each patient.
Results: 10/167 (5.9%) experienced at least one episode of AP during follow up; 10/10 were pancreatic sufficient (PS). Patients with AP/ARP showed a PIP score ≤0.25 more frequently (6/10) than patients without AP/ARP. The odds ratio (95% CI) of developing pancreatitis was 4.54 (1.22–16.92) for patients with PIP <0.25 when compared with those who have a PIP score >0.25 (p 0.0151). PIP score was correlated with sweat chloride test ($p < 0.01$).
Conclusion: PIP score, PS status and normal/borderline sweat chloride levels could be applied to predict pancreatitis development in children with CF. ARP could lead to pancreatic insufficiency.

Keywords: PIP score; Pancreatitis; Children; Cystic fibrosis

1. Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease of the Caucasian population, with an incidence of approximately 1 in every 3000 live births worldwide [1,2]. At present over 1900 mutations occur in the CFTR gene that encodes for a cAMP-regulated chloride channel. CF phenotype includes multiorgan involvement with predominant progressive respiratory disease, pancreatic insufficiency (PI) and male infertility [1,3,4]. Pancreatic status is generally related to severity of CFTR dysfunction [5,6]; as a rule PS occurs in patients carrying at least a "mild" mutation on one allele [5,6].

Recent findings have shown a wide disease heterogeneity associated with different CFTR gene class mutations. About 10% of patients show non-classic CF disease including mono or oligo-symptomatic phenotype, pancreatic sufficiency (PS) and normal/borderline sweat test [5,7].

The prevalence of pancreatitis in CF patients is higher than in general population. Due either to residual pancreatic acinar tissue and influence of modifier genes PS patients have a higher risk of symptomatic pancreatitis up to 20%, when compared with patients with CF and PI [7–11].

Acute pancreatitis (AP), as recently defined by Morinville et al. [12], is an emerging problem in pediatric population with an increasing incidence as reported in several studies (3.6–13.2 cases per 100,000 children) [13,14]. No evidence-based guidelines are currently available regarding diagnostic, natural history and treatment aspects of children with AP [12].

Etiologies of pancreatitis in children are markedly different from adults involving biliary disease, drug-induced pancreatitis,

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recurrent hereditary pancreatitis and trauma as major factors. However, up to 30% of cases remain with no defined etiology [12].

A CFTR "mild" mutation on at least one allele accounts for the residual pancreatic function; the resulting decreased ductal bicarbonate secretion predisposes to acidification of the pancreatic lumen and activation of proteolytic enzymes [10]. In CF patients with PS a residual pancreatic reserve can avoid abnormal nutrient digestion, but it may contribute to pancreatitis, due also to genetic and environmental factors. In time, recurrence of symptomatic AP may induce fibrosis and destruction of exocrine/endocrine parenchyma, leading to progression from PS to PI [15]. In CF pancreatitis is diagnosed by symptoms, such as abdominal pain associated with varying degrees of nausea and vomiting, increasing value of serum pancreatic enzyme concentrations with a variation in the agreed "cut-off" limit, and imaging evidences of acute inflammation of the pancreas [12,15]. However, in some cases these findings cannot be detected and asymptomatic AP could remain an under-recognized condition. In children, treatment is based only on symptomatic approaches with no evidence-based guidelines [12]. Few data are available for controlling and preventing acute recurrent pancreatitis (ARP); the role of lower fat intake in the diet is only partially successful. In 2011, Ooi et al. [11] introduced a new surrogate measure known as the Pancreatic Insufficiency Prevalence (PIP) score. By PIP score, a relationship between the functional severity of CFTR genotype and risk of pancreatitis was observed among patients with CF and PS [10,11]. On the basis of the PIP score value, mutations were classified as either mild (≤ 0.25) or moderate-severe (≥ 0.25) [11]: a higher PIP score is generally associated to PI–CF phenotype and a lower risk of pancreatitis, while a lower PIP score is associated with the PS–CF phenotype and a higher risk of pancreatitis.

The aims of our study were:1) to evaluate retrospectively the prevalence of pancreatitis in a cohort of children with CF; 2) to correlate this prevalence to pancreatic status, CFTR gene mutations and sweat chloride level; and 3) to test the potential role of PIP score as a tool to predict risk of pancreatitis in children with CF and rare mutations.

2. Methods

185 pediatric CF patients [median age ± standard deviation (SD): 11.4 ± 5.3, range 1.1–18 years] were evaluated for recruitment in the study. 18/185 (9.7%) were ruled out since CFTR analysis failed to identify mutations on both alleles and PIP score could not be determined. We examined 167 patients with CF (79 males, median age ± SD 11.8 ± 5.9, range 1.3–18 years) in regular follow up at the CF Regional Care Centre of Naples, Italy. CF diagnosis was based on suggestive clinical symptoms, quantitative pilocarpine iontophoretic sweat chloride concentrations over 60 mmol/l and/or identified CFTR mutations on both alleles, according to the current consensus reports [5,16]. The analysis of all CFTR coding regions (27 exons and intron–exon boundaries) was performed by gene sequencing (detection rate 94%).

A record of demographic, genetic and biochemical data regarding all our CF patients is regularly available in a computerized database in our Care Center. All medical records of patients in follow-up from December 2002 to December 2012 were retrospectively evaluated for the study. Status of PS was defined on the basis of fecal pancreatic elastase higher than 200 mcg/g [17,18] measured outside of AP.

Episodes of AP and ARP were extracted from database in order to define their prevalence. On the basis of presence/absence of AP/ARP we identified two groups of patients who were compared for age at CF diagnosis, clinical features, genotypes and sweat chloride level.

AP was defined as requiring at least 2 of the following criteria: abdominal pain compatible with pancreatitis (with no other attributable cause), serum amylase and/or lipase values ≥ 3 folds higher than the upper limit of the reference range, imaging evidence of acute (such as pancreatic edema, hemorrhage, or necrosis) or chronic pancreatitis (such as calcification or characteristic ductal changes), as previously described [12]. Episodes of pancreatitis concerning other etiologies were ruled out.

Clinical data were scheduled as age of onset and number of pancreatitis, during the observation period, pancreatitis risk factors such as drugs, acute infections, complications as pseudocyst, abscess, retroperitoneal hemorrhage and hypocalcemic tetany, as well as imaging evidences by ultrasonography, computerized tomography, or endoscopic retrograde cholangiopancreatography, detected during episodes of pancreatitis.

Patients with PS phenotype were monitored to detect a progression to PI, once a year or more when suggestive symptoms occurred.

2.1. Pancreatic Insufficiency Prevalence (PIP) score

PIP score has been recently developed and validated [11]. It was based on the prevalence of PI in a large and well-defined cohort of CF patients. We calculated PIP score for each mutation as ratio between PI patients carrying a single mutation and all PI and PS patients carrying the same mutation both in a homozygous state and in a heterozygous state compound with mutations known to have severe consequences. Data were compared with those of Ooi et al. [11,12]. We considered CF mutation as mild when PIP score was ≤ 0.25 and moderate-severe when PIP score was >0.25, according to the cut-off value suggested by the Canadian Consortium for CF Genetic Studies (CCCFGS) [11].

Subsequently we estimated the PIP score of each enrolled patients.

2.2. Statistics

Data with a Gaussian distribution were compared by an independent Student t test, Pearson analysis was used to evaluate correlation between factors, while Chi-Square test was used for non-normal data. Level of significance was set at $p < 0.05$. Data analysis was performed using SPSS software (17.0).

3. Results

3.1. Clinical characteristics

A flow-chart of enrolled study population was shown in Fig. 1. 10/167 children (5.9%) experienced at least one episode of AP during the observational period. 54/167 (32.3%) patients were classified as PS. All patients with pancreatitis were PS (10/54 [18.5%]). In the PS group CF diagnosis was generally performed later than patients with PI (median age ± SD: 3.0 ± 5.1 vs. 1.19 ± 2.12 respectively; $p < 0.05$). Symptoms at diagnosis were respiratory acute disease in 23, AP or ARP in 4, recurrent abdominal pain in 2, hyponatriemic dehydration in 3, failure to thrive in 2 and nasal polyposis in one; 9 patients were diagnosed by newborn screening (NBS) and 10 for familiarity. 38/54 PS children (70.3%) had normal or borderline sweat chloride level. As expected, mean sweat-chloride levels were lower in PS than in PI patients (M ± SD: 46.2 ± 31.4 vs. 96.0 ± 13.6 respectively; $p < 0.001$).

Among studied patients genetic analysis showed: 40/167 (24%) F508del/F508del, 63/167 (34%) F508del/other and 64/167 (38%) other/other. Two out of 167 enrolled patients were compound heterozygous for I148T (F508del/I148T; G85E/I148T). CF diagnosis was based on suggestive clinical symptoms, sweat chloride levels > 60 mmol/l (85 and 114 mmol/l respectively) and PI (fecal elastase < 100 mcg/g). Complex alleles were ruled out.

Episodes of pancreatitis were detected at a mean age of 5.2 years (range 1–12.7 years). None of our patients showed complications during the follow up (7.8 years, range 1.1–15.8) but 1/10 developed PI 6.5 years later than the first episode of AP. Patients with pancreatitis had a sweat chloride mean level lower than patients without pancreatitis (M ± SD: 50.0 ± 34.5 vs. 81.8 ± 30.3; $p < 0.05$).

Clinical characteristics of patients with CF and pancreatitis are shown in Table 1.

3.2. PIP score results

Table 2 shows PIP score results compared with those of Ooi et al. Based on PIP score we divided patients into two groups: 122 out of 167 (73%) had a PIP score >0.25 [9/122 (7.3%) with PS and 113/122 with PI], while 45 out of 167 (27%) had a PIP score <0.25 (45/45 with PS). Among patients with PIP score >0.25 only 2/122 (1.6%) patients had normal or borderline sweat chloride test, while 38/45 (84.4%) with PIP score <0.25 showed a normal or borderline sweat chloride test with a significant statistical difference ($p < 0.001$), as shown in Table 3. Despite that the two groups were not comparable for sample size, we registered that patients with pancreatitis had a PIP score lower than patients without pancreatitis [M ± SD: 0.31 ± 0.41 vs. 0.66 ± 0.39; $p < 0.001$]; moreover the number of patients with PANC was higher among those with PIP score <0.25 when compared with those with PIP score >0.25 [6/10 (60%) vs. 39/157 (24.8%)]. The odds ratio (95% CI) of developing pancreatitis was 4.54 (1.22–16.92) for patients with PIP <0.25 when compared with those who have a PIP score >0.25 (p 0.0151). A significant correlation between PIP score and sweat chloride levels (Pearson correlation 0.829, p value <0.001) (Fig. 2) was observed.

4. Discussion

In the last years an increasing percentage of patients with CF have been described as having non-classic forms of CF [8]. These cases are generally characterized by a later onset of symptoms such as pancreatitis, disseminated bronchiectasis, congenital bilateral absence of vas deferens associated to

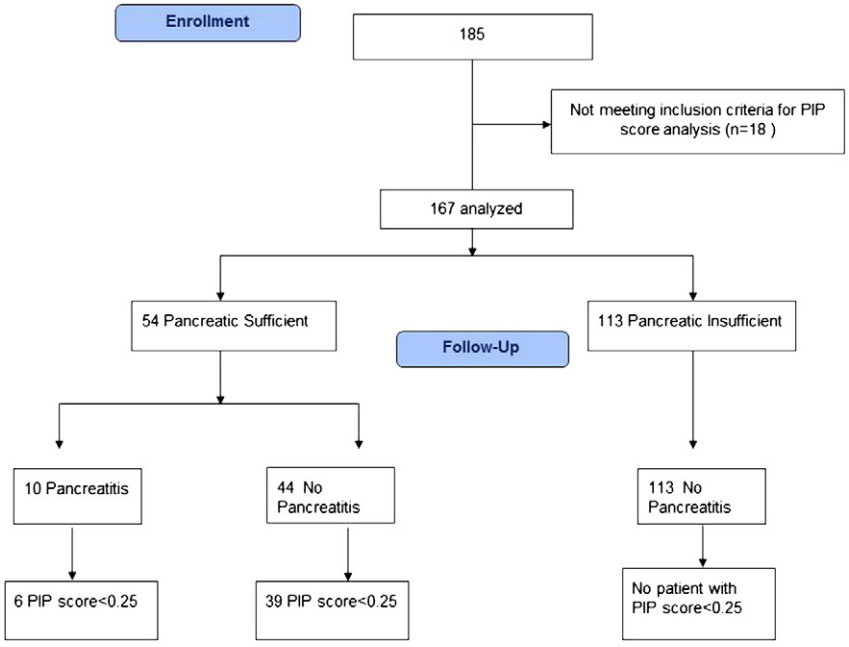

Fig. 1. Study population.

Table 1
PIP score for most frequent CFTR mutations in our cohort of patients.

CFTR mutation	Total PI	Total PI + PS	PIP score Naples CF center	PIP score Canadian consortium
G542X	17	17	1.00	0.99
CFTRdel2,3	3	3	1.00	1.00
1717-1G > A	3	3	1.00	0.95
R1066C	3	3	1.00	0.83
I148T	2	2	1.00	0.91
711 + 1G > T	2	2	1.00	1.00
R1158X	2	2	1.00	1.00
G1244E	2	2	1.00	N.D.
Y849X	2	2	1.00	N.D.
L732X	2	2	1.00	N.D.
17a-17b-18del	2	2	1.00	N.D.
E193X	2	2	1.00	1.00
N1303K	15	16	0.94	0.95
F508del	78	85	0.92	0.96
W1282X	8	9	0.88	0.95
2183AA > G	7	8	0.87	1.00
4016insT	4	5	0.80	1.00
G85E	4	6	0.67	0.73
D759G	2	3	0.66	0.00
G178R	2	3	0.66	0.00
3131del15	1	2	0.50	N.D.
2789 + 5G > A	1	2	0.50	0.38
(TG)12(T)5	0	8	0.00	N.D.
L977F	0	6	0.00	N.D.
D1152H	0	6	0.00	N.D.
V201M G/A	0	2	0.00	N.D.
3849 + 10kbC > T	0	2	0.00	0.09
R74W	0	2	0.00	N.D.
R117H	0	2	0.00	0.04
R334W	0	2	0.00	0.10

Abbreviations: PIP = Pancreatic Insufficiency Prevalence, PI = Pancreatic Insufficiency, PS = Pancreatic Sufficiency.

normal or borderline sweat chloride concentrations and two CF-causing mutations with variability of CFTR protein dysfunction. In this group an increasing percentage of patients with CF and PS (about 27.5%) has been described [8]. We suppose that both the increase of sensitivity of diagnostic molecular tests for CF and early diagnosis by NBS have contributed to detect non-classic CF disease.

Table 3
Relation between sweat test results and PIP score values.

Sweat test (Cl^-)	PIP score > 0.25	PIP score < 0.25
Normal <40 mmol/l	0	30
Borderline 40–60 mmol/l	2	8
Pathological >60 mmol/l	120	7

Abbreviations: PIP = Pancreatic Insufficiency Prevalence.

A severe dysfunction of CFTR protein causes already in utero, a progressive damage of acinar pancreatic tissue leading to pancreatic acinar atrophy up to PI when >98% of pancreatic parenchyma has been destroyed [8–11]. A residual function of CFTR protein related to "mild" CFTR mutations could reduce fluid pancreatic secretion and trypsinogen/trypsin wash-out [19], preserving pancreatic enzymes secretion. Persistence of normal residual acinar pancreatic tissue may favor pancreatitis. This event has been previously reported as a relatively rare finding (prevalence of 1.24%) [9] in all CF children. Nevertheless, an increased incidence and prevalence of non-classic CF, according to increasing median life expectancy, may determine a higher prevalence (up to 14–17%) of pancreatitis in adult CF patients with PS [7,8]. In all pediatric patients in regular follow-up at our CF center we registered a prevalence of PS of 29.1% (Fig. 1). Our data highlight a prevalence of pancreatitis of 5.9% in CF children regardless of pancreatic status and of 18.5% in PS subgroup, that is higher than previously reported [9]. Moreover, according to Durno et al. and Augarten at al. [7,8], all patients with pancreatitis were PS.

We have applied the PIP score regardless of pancreatic status in order to verify whether PIP score may help to early predict the risk of pancreatitis, also in children diagnosed by NBS. We found that a lower PIP score may predict the risk of pancreatitis, confirming that more frequently a mild mutation may predispose to pancreatitis. In particular, patients with a PIP score ≤ 0.25 had pancreatitis and at least a mild mutation on one allele more frequently than patients with PIP score >0.25 without pancreatitis and a moderate-severe mutation (60.0% vs. 24.8%, respectively).

Moreover, in our cohort of patients we found a significant correlation between values of PIP score and sweat chloride

Table 2
Clinical characteristics of patients with CF and pancreatitis.

No.	Age at CF diagnosis	Presenting symptoms at diagnosis	PI	Age at first P	No. of P	Genotype	Sweat chloride value (mmol/l)	PIP score
1	7 y	P	No	5 y/6 m	>2	E193X/L997F	24	0
2	13 y	P	No	11 y	>2	G542X/L997F	22	0
3	3 m	FT, RTI	No	1 y/6 m	>2	3849 + 10kbC- > T/G1244E	27	0.09
4	10 m	RAP	No	2 y/3 m	>2	2183AA-G/W1282X	83	0.87
5	10 y	P	No	8 y	>2	N1303K/D579G	100	0.66
6	8 m	RTI, LD	No to Yes	6 y	>2	F508del/3131del15	90	0.50
7	14 m	P, RTI	No	1 y	<2	DeltaF508/D1152H	30	0
8	5 m	MA, P	No	3 y	>2	F508del/G85E	85	0.67
9	2 m	NS	No	1 y/2 m	<2	R117H/R334W	18	0
10	13 y	P	No	12 y/7 m	<2	D1152H/Y849X	16	0

Abbreviations: CF = Cystic Fibrosis, P = pancreatitis, FT = failure to thrive, RTI = recurrent tract infections, RAP = recurrent abdominal pain, LD = liver disease, MA = metabolic alkalosis, NS = newborn screening.

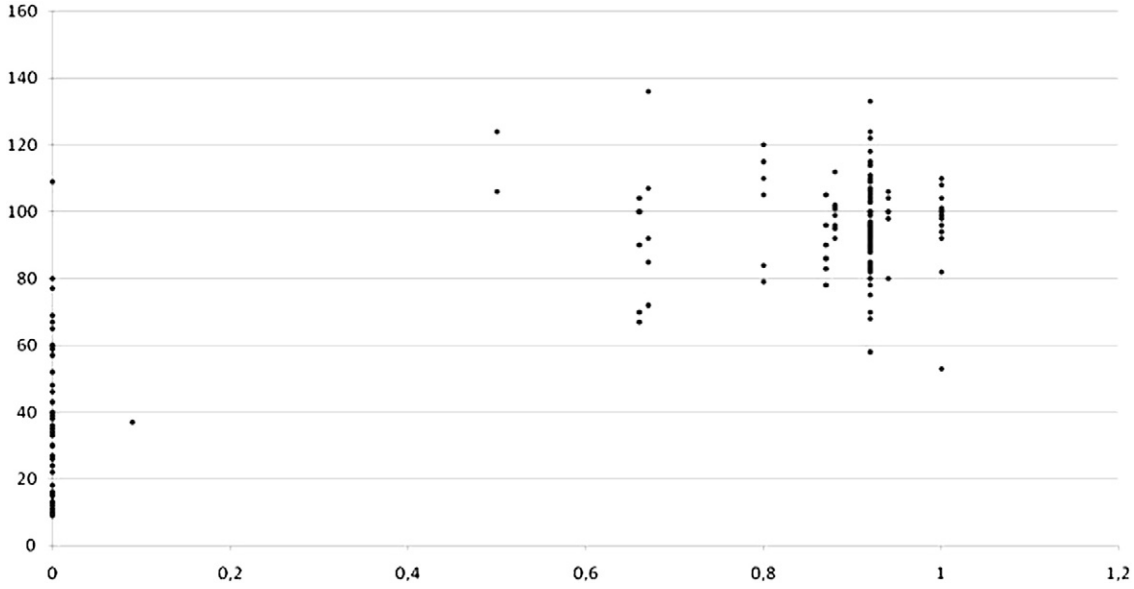

Fig. 2. Correlation between PIP score and chloride sweat level.

concentration, confirming that sweat chloride levels concentrations is well-representative of CFTR function.

As previously described, a small proportion of PS patients carrying severe mutations on both alleles may have a high risk to progressively develop PI [9,11,20,21]. In our cohort of patients 4/122 (3.2%) with CF severe mutations on both alleles sweat chloride concentrations over 60 mmol/l and PIP score >0.25 presented ARP; among them one patient experienced ARP developing PI 6.5 years later the first episode of pancreatitis, much earlier than data previously reported on risk of PS-PI progression [11]. So far, we underline that a careful monitoring of pancreatic function is recommended, especially for those patients with severe CFTR mutations who experience pancreatitis in childhood.

On the basis of our preliminary results we suggest that PIP score should be applied to predict the risk of pancreatitis in children with CF, from diagnosis. Our findings could promote diagnostic and therapeutic programs in patients at risk of pancreatitis (PIP < 0.25) in order to prevent pancreatic disease progression.

As reported by Ooi, the occurrence of mild mutations on both alleles may confer a significantly higher cumulative proportion and greater risk of pancreatitis than those with mild/severe and severe/severe allele combinations [10,11], but we were not able to verify this association because the follow up of our patients has been restricted to pediatric population.

Current clinical practices recommend an early detection of patients at risk of pancreatitis in order to improve their own lifestyle for preventing recurrence of AP and controlling progression of pancreatic disease.

Nowadays it is difficult for pediatricians to establish the follow up of pancreatitis and reassure the families as regards their kid's future. In these cases, an available standardized score which predicts the risk of pancreatitis could be a useful tool for clinical practice.

Despite the small sample size and a shorter follow-up of this retrospective observational study, our data are in agreement with those of Ooi. We suggest that PIP score, sufficient pancreatic status and normal/borderline sweat chloride levels could be applied in order to predict the risk of developing pancreatitis in children with CF.

PIP score has potential for other applications also including predicting PI phenotype and classifying patients with either severe or mild genotypes irrespective whether, but especially when, the mutation class is unknown.

We also encourage larger epidemiological studies in order to validate the role of this score in children with other hereditary pancreatitis [15,22–24].

Conflict of interest statement

Authors declare no conflict of interest.

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